A Mild and Highly Efficient Conversion of Arylboronic Acids into Phenols by Oxidation with MCPBA

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Abstract: A mild and highly efficient synthesis of phenols from arylboronic acids in a H_2O -EtOH (1:2) solution was achieved by using MCPBA as the oxidant at room temperature. Isotopical labeling studies had shown that the hydroxyl oxygen atom of the phenol might originate from the MCPBA.

Key words: arylboronic acids, efficiency, MCPBA, oxidation, phenols

Phenols are widely used as versatile intermediates and employed in the synthesis of natural products, materials, and biological and pharmaceutical compounds.¹ Phenols are usually prepared from aryl halides through a nucleophilic substitution or by metal-catalyzed hydroxylation, and copper-catalyzed transformations of diazoarenes are also applied in the laboratory.² In recent years, several methods have been established to convert arylboronic acids into phenols with or without metal catalysis.³ Aqueous hydrogen peroxide,^{3h-j} oxone,^{3k} molecular oxygen (or air),^{3d,1} and sodium perborate^{3m,n} had been applied as oxidants for the hydroxylation of arylboronic acids. These transformations were often carried out under basic (alkali base) or neutral conditions.

MCPBA (*m*-chloroperbenzoic acid) is widely used as an electrophilic reagent capable of reacting with many functional groups, and it can deliver oxygen to alkenes, sulfides, selenides, and amines.⁴ Herein, we report the first use of MCPBA as an oxidant to convert arylboronic acids into phenols efficiently at room temperature without any alkali base, metal catalyst, or ligand.

Studies were initiated in a H_2O -EtOH (1:1) solution using MCPBA as the oxidant at room temperature. The result was promising, and the yield of phenol increased to 84% (Table 1, entry 1). Increasing the amount of ethanol in the H_2O -EtOH solution resulted in a higher yield of product (98%, Table 1, entry 2). However, a further increase of ethanol (Table 1, entry 3) or using pure water (Table 1, entry 4) or pure ethanol (Table 1, entry 5) separately resulted in a decreased yield of phenol. This indicated that the concentration of ethanol had a significant effect on the reaction efficiency. Studies on the effect of other solvents (Table 1, entries 6–8) showed that using THF, MeCN, and MeOH resulted in a lower yield of phenol. When other ox-

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idants were employed, such as $K_2S_2O_8$, O_2 , and *tert*-butyl hydroperoxide (TBHP, Table 1, entries 9–11), phenylboronic acid was not consumed completely, and only 5–15% yield of the desired product was obtained within six hours. Phenol was obtained in moderate yield by using H_2O_2 (30%) as oxidant (Table 1, entries 12 and 13). Hence, the best conditions are shown in entry 2 (Table 1).

 $\label{eq:condition} \begin{array}{l} \textbf{Table 1} & \text{Optimization of the Reaction Conditions for the Hydroxyl-ation of Phenylboronic Acid^a} \end{array}$

B(OH) ₂ oxidant, solvent			
√ 1a		~ 2a	
Entry	Oxidant	Solvent	Yield of 2a (%) ^b
1	МСРВА	H ₂ O–EtOH (1:1)	84
2	MCPBA	H ₂ O–EtOH (1:2)	98
3	MCPBA	H ₂ O–EtOH (1:4)	86
4	MCPBA	H ₂ O	70
5	MCPBA	EtOH	82
6	MCPBA	H ₂ O–THF (1:2)	86
7	MCPBA	H ₂ O–MeCN (1:2)	88
8	MCPBA	H ₂ O–MeOH (1:2)	89
9	$K_2S_2O_8$	H ₂ O–EtOH (1:2)	5
10	O ₂	H ₂ O–EtOH (1:2)	5
11	TBHP	H ₂ O–EtOH (1:2)	15
12	H_2O_2	H ₂ O	63
13	H_2O_2	H ₂ O–EtOH (1:2)	69

^a Reaction conditions: phenylboronic acid (0.5 mmol) and oxidant (0.5 mmol) in solvent (2 mL)⁵ at r.t., 6 h, air.

^b Yield determined by ¹H NMR spectroscopy.

Subsequently, a variety of boronic acids were examined to generate the hydroxylation products under the optimized conditions. The results are summarized in Table 2. The substituted aromatic boronic acids bearing electron-deficient or electron-rich groups were converted into the corresponding phenols smoothly in good to excellent yields. *p*-Cyanophenol, *m*-nitrophenol, *p*-chlorophenol, *p*-tert-buylphenol, and 1-naphthol were obtained in yields of above 95%. The functional groups which are easily oxi-

dized,³¹ including methylthio and aldehyde, were tolerated in these mild processes. More importantly, the electronrich phenols such as *p*-methoxyphenol, 2,6- dimethylphenol, and *p-tert*-buylphenol, which are difficult to obtain from the traditional nucleophilic substitution of aryl halides, could be easily generated using this method. The substrate scope of this methodology had been extended to the phenylboronic pinacol ester **1k** and cyclohexylboronic acid **1**. And the desired products **2a** and **2** were obtained in 96% and 60% yield after six hours, respectively (Scheme 1). However, the heteroarylboronic acids, for example, 4-pyridinylboronic acid, 2-furanylboronic acid, and 3-thiopheneboronic acid, were not suitable for this reaction.

Table 2 Hydroxylation of Arylboronic Acids in Aqueous Ethanol

 Solution^{a,b}



Table 2Hydroxylation of Arylboronic Acids in Aqueous EthanolSolution^{a,b}(continued)





^b Isolated yield.



Scheme 1

In the interest of elucidating the reaction process, we first considered the source of phenolic oxygen, so a preliminary mechanistic study with isotope-labeled water ($H_2^{18}O$) was performed (Scheme 2). When the reaction of phenylboronic acid was carried out employing $H_2^{18}O$ ($H_2^{18}O$ content: >40%) as a solvent under the optimal reaction conditions, incorporation of ¹⁸O into the phenol was not observed by HRMS analysis, which implied that the oxygen source for the phenol formation was not water.⁶ The same yield was obtained when the control reaction was carried out under an N₂ atmosphere (Scheme 3), suggesting that molecular oxygen was not crucial for the process and the oxygen source for the phenol formation was not O₂.

Hence, based on the above observation, the source of phenolic oxygen might be from MCPBA. The mechanism of



the oxidative hydroxylation of phenylboronic acid was hypothesized (Scheme 4), as suggested by the recently reported work on the mechanism studies of the aerobic oxidative hydroxylation of arylboronic acids through photoredox catalysis.^{3d} Firstly, **1a** reacted with MCPBA to generate the intermediate **3a**, then rearrangement of **3a** afforded a phenolic species **4a**. Finally, the hydroxylated product **2a** was obtained by hydrolysis of **4a**.



Scheme 4 The proposed mechanism of the reaction

In conclusion, a highly efficient synthesis of phenols⁷ from arylboronic acids has been developed by using MCPBA as an oxidant. The process employed a mixture of water and ethanol as the reaction medium. It is a mild and simple reaction under metal-, ligand-, and base-free conditions. Further investigations to determine the mechanism of the reaction and to expand their scope are under way in our laboratory.

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General Procedure for the Hydroxylation of Phenylboronic Acid To the mixture of phenylboronic acid (0.5 mmol) in a H₂O– EtOH (1:2) solution (2 mL) in a round-bottom flask was added MCPBA (0.5 mmol) at r.t. When phenylboronic acid was completely consumed (monitored by TLC, 6 h), 0.1 M aq NaHCO₃ (5 mL) was added to the mixture. Then the reaction mixture was extracted with EtOAc (2×15 mL). The combined organic layer was washed with H₂O (10 mL) and brine (5 mL), dried over anhyd MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (PE–EtOAc = 4:1), and the corresponding phenol was obtained as a colorless solid (**2a**, 46 mg, 97%). Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.